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SYSTEMIC REVIEW OPEN ACCESS

A Systematic Review and Model-Based Meta-Analysis of Pegylated-Interferon-α-Induced HBsAg Loss in Chronic Hepatitis B Virus Infection

Nathan J. Hanan[1] | Matthew L. Zierhut[2] | Ahmed Nader[1] | Anadi Mahajan[3] | Amandeep Kaur[3] | Krishna Kumar[3] | Susan A. Dixon[4] | Joyeta Das[4] | Mindy Magee[1] | Dickens Theodore[5] | Vera Gielen[4]

[1]GSK, Collegeville, Pennsylvania, USA | [2]Certara, San Diego, California, USA | [3]Bridge Medical Consulting, London, UK | [4]GSK, Middlesex, UK | [5]GSK, Durham, North Carolina, USA

Correspondence: Nathan J. Hanan (nathan.j.hanan@gsk.com)

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ABSTRACT

Pegylated-interferon-α (Peg-IFNα) is a treatment option for chronic hepatitis B virus (HBV) infection. To quantify treatment response variability, we conducted a model-based meta-analysis (MBMA) of hepatitis B surface antigen (HBsAg) loss, defined as a binary outcome based on HBsAg levels falling below the limit of detection, with Peg-IFNα-based regimens at end-of-treatment (EOT) and 24 weeks post-treatment. A systematic review of HBsAg loss in chronic HBV infection was performed, searching Embase, MEDLINE, and Cochrane (January 2000–July 2022). Studies reporting only per-protocol results were excluded; intent-to-treat (ITT) or modified ITT results were prioritized. Models described the proportion achieving HBsAg loss with respect to treatment regimens, exploring baseline clinical and demographic covariates. For the EOT model, 83 study-strata-arms (11,493 participants) were included; for the 24-week model, 58 study-strata-arms (4267 participants) were included. In both models, Peg-IFNα duration and baseline HBsAg significantly predicted HBsAg loss ($p < 0.001$); baseline hepatitis B e-antigen (HBeAg) was an additional predictor at EOT ($p = 0.007$). These covariates reduced between-trial variance by 58.1% (EOT) and 77.6% (24-week), highlighting their role in explaining heterogeneity. This MBMA supports clinical trial design by simulating outcomes with Peg-IFNα across diverse populations, optimizing trial parameters, estimating sample sizes, and informing enrichment strategies. Notably, these findings have been applied to calibrate and validate in silico trials, demonstrating utility in advancing computational approaches for HBV drug development. This approach enhances precision in predicting treatment outcomes and sets a precedent for leveraging MBMA in chronic hepatitis B research, paving the way for more effective strategies.

1 | Introduction

Chronic hepatitis B virus (HBV) infection remains a significant global health burden, affecting an estimated 257.5 million people worldwide in 2022 and contributing to 820,000 deaths annually due to cirrhosis and hepatocellular carcinoma (HCC) [1]. It is also associated with stigma, discrimination, and extrahepatic manifestations [2]. Notably, 50% of all deaths due to HCC are linked to chronic HBV infection [3]. The primary goal of HBV treatment is to achieve a functional cure, defined as sustained

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Study Highlights

- What is the current knowledge on the topic?
  - Hepatitis B surface antigen (HBsAg) loss is the primary goal of chronic hepatitis B (CHB) treatment, as it is linked to an improved prognosis. Pegylated-interferon-α (Peg-IFNα) generally achieves higher HBsAg loss rates compared to nucleos(t)ide analogues (NAs) in broader populations, with even greater success observed in certain favorable patient groups, depending on factors like hepatitis B e-antigen status, prior NA treatment, and baseline HBsAg levels. For example, in some NA-suppressed patients with low baseline HBsAg levels treated with Peg-IFNα as a switch or add-on therapy, significantly higher rates of HBsAg loss have been reported. However, responses vary widely across populations and treatment regimens.
- What question did this study address?
  - This study investigated predictors of HBsAg loss in CHB patients treated with Peg-IFNα–based regimens at end of treatment (EOT) and 24 weeks post-treatment and quantified between-trial variability using model-based meta-analysis (MBMA).
- What does this study add to our knowledge?
  - This MBMA identified treatment duration, baseline HBsAg, and HBeAg status as key predictors of HBsAg loss, substantially reducing unexplained variability across trials. These findings provide a quantitative framework for understanding Peg-IFNα response heterogeneity and support more personalized treatment strategies.
- How might this change drug discovery, development, and/or therapeutics?
  - The MBMA enables simulation of trial outcomes, sample size estimation, and enrichment strategies based on patient characteristics, thereby informing clinical trial design and advancing model-informed drug development in CHB.

hepatitis B surface antigen (HBsAg) loss and HBV DNA suppression for at least 6 months after treatment cessation, with or without seroconversion, as this outcome reduces the risk of disease progression, including cirrhosis, liver transplantation, HCC, and death [4–8]. Recent studies demonstrate that HBsAg loss, a key component of functional cure, significantly lowers HCC risk compared to persistent HBsAg positivity [9–13].

Currently approved therapies for chronic HBV infection include nucleos(t)ide analogues (NAs) and pegylated-interferon-α (Peg-IFNα). NAs, the standard of care, effectively suppress viral replication but often require lifelong use, while Peg-IFNα, typically administered as a 48-week regimen, offers immune-mediated control and higher HBsAg loss rates (2.4%–8.3% in general populations, with rates ranging from 17% to 56.1% in favorable subpopulations, depending on hepatitis B e-antigen (HBeAg) status, prior NA treatment, and baseline HBsAg levels) despite tolerability challenges [14–17]. Notably, in NA-suppressed HBeAg-negative patients with detectable baseline HBsAg levels ranging from 0.05 IU/mL (the limit of detection) to 100 IU/mL ($\log_{10} = 2$), such as those in the EVEREST Project treated with Peg-IFNα as a switch or add-on therapy, HBsAg loss rates reached 56.1% at 48 weeks, highlighting the potential for higher clearance in these subpopulations [15]. However, achieving a functional cure remains elusive due to the persistence of covalently closed circular DNA (cccDNA) in hepatocytes and immune exhaustion, which contribute to the low and variable HBsAg loss rates observed with current therapies [7]. HBsAg loss rates with Peg-IFNα-based regimens vary widely due to differences in patient characteristics, treatment regimens, and trial design factors [14]. Understanding this variability is critical for optimizing treatment strategies and enhancing clinical trial design. Traditional meta-analyses often fail to account for between-trial heterogeneity or the impact of covariates on treatment response, whereas a model-based meta-analysis (MBMA) provides a robust framework to integrate data across studies, quantify variability, identify predictors, and enhance precision in predicting treatment outcomes. Additionally, MBMA can support the development of novel therapeutic approaches by providing benchmark data for evaluating new regimens, as demonstrated by its recent application in calibrating in silico trials for HBV [18]. By addressing this gap, our study not only advances precision in HBV treatment but also sets a foundation for future research into functional cure strategies. Here, we conducted the first MBMA of HBsAg loss with Peg-IFNα-based regimens at end-of-treatment (EOT) and 24 weeks post-treatment to elucidate key predictors, quantify variability, and provide a predictive tool for clinical trial design in chronic HBV infection.

2 | Methods

2.1 | Identification, Selection, and Extraction of Studies

A systematic literature review (SLR) was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology to identify studies reporting HBsAg loss in patients with chronic HBV infection treated with Peg-IFNα-based regimens. A comprehensive search strategy was designed to retrieve relevant citations from published literature, spanning Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica Database (Embase) via Embase.com, as well as the Cochrane database, from January 2000 to July 2022. The search was supplemented by gray literature searches, back-referencing of primary studies and review articles, and hand-searching of relevant conference abstracts from 2020 to 2022, including those from the Asian Pacific Association for the Study of the Liver (APASL), American Association for the Study of Liver Diseases (AASLD), and European Association for the Study of the Liver (EASL). Inclusion and exclusion criteria are detailed in Table S1. Studies were screened to include observational studies (prospective and retrospective cohort studies) and clinical trials in representative populations of patients with chronic HBV infection. The title and abstract of each record were assessed for relevance, followed by a detailed full-text review to determine inclusion. Each publication was evaluated, and data were extracted by two independent reviewers, with discrepancies resolved by a third reviewer. Extracted parameters included study characteristics,

treatment details, patient baseline characteristics, and HBsAg loss outcomes.

2.2 | Derivation of the Analysis Subsets

For the MBMA, studies identified in the SLR were refined to focus on HBsAg loss, defined as a binary outcome (achieved vs. not achieved) based on HBsAg levels falling below the assay's limit of detection. Two endpoints were analyzed: HBsAg loss at the end of treatment (EOT) with Peg-IFNα, and HBsAg loss at 24 weeks post-IFN-α cessation, as a surrogate for functional cure (sustained HBsAg and HBV DNA loss for 6 months post-cessation of all antiviral therapy). Studies were included if they reported HBsAg loss at EOT and/or 24 weeks post-treatment, while results at other time points (e.g., 3 months post-treatment) were excluded.

A study–strata–arm was defined as the observation unit, representing a specific treatment arm within a study that could be further stratified by patient characteristics such as HBeAg status, baseline HBsAg, or baseline HBV DNA. When no stratification was performed, the study-arm was equivalent to the study–strata–arm. For example, a study with two treatment arms stratified by HBeAg-negative or HBeAg-positive participants would yield four observations (one study × two strata × two arms). This structure allowed stratified data to be integrated while preserving granularity.

The study–strata–arms included in the analysis comprised either Peg-IFNα monotherapy or Peg-IFNα plus NA combination therapy, where participants in the combination arms may have stopped or continued NA after cessation of Peg-IFNα. Studies were excluded if they investigated non-standard Peg-IFNα dosing, employed non-standard definitions of HBsAg loss, or did not report baseline HBeAg status. To minimize inflation of treatment effects, studies reporting only per-protocol (PP) results were excluded, with intent-to-treat (ITT) or modified intent-to-treat (mITT) results prioritized. Because few trials reported HBsAg loss at both EOT and 24 weeks post-IFN-α cessation, and very few reported intermediate or longer-term follow-up, two cross-sectional models were developed rather than a longitudinal trajectory model.

Covariates were derived to evaluate their association with HBsAg loss. Continuous covariates (age, baseline HBsAg, treatment duration) were modeled using study–strata–arm means or medians and centered to the population median to facilitate interpretation. Binary covariates included gender, baseline HBeAg status, and continuation of NA after Peg-IFNα cessation (24-week model only), based on whether study protocols permitted NA continuation. This last variable was included due to evidence that some patients achieve HBsAg loss following NA cessation, potentially influencing sustained HBsAg loss post-Peg-IFNα [19–21]. Study design was coded as randomized controlled trial (RCT) versus non-RCT, where the latter category included prospective and retrospective cohort studies and single-arm trials.

Three covariates required more detailed derivation. Baseline HBsAg was taken as the reported median $\log_{10}$ IU/mL when available, or the mean when only mean values were reported. If baseline HBsAg was reported as tightly defined strata (e.g., 0–500, 500–1000, 1000–1500 IU/mL), the midpoint of each stratum was used. Studies reporting only broad non-continuous categories (e.g., <3000 vs. >3000 IU/mL) were excluded due to unreliable imputation. Race was defined as the study–strata–arm proportion of non-Asian participants, ranging from 0 (100% Asian) to 1 (100% non-Asian). Study design was classified as RCT versus non-RCT, with non-RCTs comprising prospective and retrospective cohort studies and single-arm trials.

Data processing and covariate derivations were performed in R (version 4.2.1) using the "tidyverse" package library.

2.3 | Model Building

Models were developed using R (version 4.2.1) with the "nlme" package. Two efficacy endpoints were analyzed independently: HBsAg loss at the end of treatment (EOT) and HBsAg loss at 24 weeks post-EOT. Model development followed a stepwise process consistent with MBMA methodology, progressing from structural base models to treatment-effect models, and then to a final covariate model.

2.3.1 | Base Model

As a binary endpoint, HBsAg loss was assumed to follow a binomial distribution. Let p_{isa} denote the probability of HBsAg loss for study i, stratum s, and treatment arm a. The base model described this probability using a logistic formulation:

$$p_{isa} = \text{logit}^{-1}\left(\mu + \eta_{isa}\right) + w_{isa} \cdot \varepsilon_{isa}$$

where μ is the overall treatment effect on the logit scale, representing the average log-odds of HBsAg loss across all treatment regimens at this stage. $\eta_{isa} \sim N\left(0,\ \sigma_{\eta}^2\right)$ is a random effect capturing between–study–strata–arm heterogeneity. ε_{isa} is the residual error term representing within–study–strata–arm sampling variability. The residual variance was fixed to $\sigma^2 = 1$, so that the error term acts as a standardized sampling error, consistent with the binomial distribution. Because each observation represents a binomial proportion, variability was modeled with a variance function proportional to:

$$w_{isa} = \sqrt{\frac{\hat{p}_{isa} \cdot \left(1 - \hat{p}_{isa}\right)}{N_{isa}}},$$

where $\hat{p}_{isa}$ is the model-estimated probability of HBsAg loss and N_{isa} is the sample size for study–strata–arm (i, s, a). This formulation avoids double-counting variance and ensures that predicted probabilities remain bounded between 0 and 1.

2.3.2 | Treatment-Effect Model

The base model was then extended to account for treatment-specific effects, distinguishing Peg-IFNα monotherapy from Peg-IFNα + NA combination therapy:

$$p_{isa} = \text{logit}^{-1}\left(\text{drug. eff}_d + \eta_{isa}\right) + w_{isa} \cdot \varepsilon_{isa}$$

where drug. eff_d is the fixed effect associated with drug regimen d. At this stage, the model estimated separate mean log-odds of HBsAg loss for each treatment group.

2.3.3 | Final Covariate Model

A covariate analysis was then performed to evaluate whether biological, demographic, or trial design characteristics explained variability in treatment response across study–strata–arms. Continuous covariates (e.g., baseline HBsAg) were centered to the median value across study–strata–arms, so that treatment effects could be interpreted at typical values. Binary covariates (e.g., HBeAg positivity) were included as indicator variables.

The final model incorporated covariates additively on the logit scale:

$$p_{isa} = \text{logit}^{-1}\left(\text{drug. eff}_d + \sum_{m=1}^{M} \beta_m \cdot \theta_{m,isa} + \eta_{isa}\right) + w_{isa} \cdot \varepsilon_{isa}$$

where $\theta_{m,isa}$ are the covariates for study–strata–arm (i, s, a). β_m are regression coefficients quantifying the effect of covariates on treatment response. Because continuous covariates were centered, the estimated treatment effects (drug. eff_d) reflect a "typical" study–strata–arm at the median values of continuous covariates and the reference levels of categorical covariates.

The impact of covariates was assessed by evaluating reductions in between–study–strata–arm variance (σ^2_η) between the base model and the final model. The percentage reduction was calculated as:

$$\text{Reduction}\,(\%) = \frac{\sigma^2_{\eta,\text{base}} - \sigma^2_{\eta,\text{final}}}{\sigma^2_{\eta,\text{base}}} \times 100$$

This reduction was reported for both the EOT and 24-week post-treatment models. Prediction intervals (95%) for fixed effect estimates, reflecting both parameter uncertainty (via the variance–covariance matrix of fixed effects) and between-trial variability (via η_{ij}), were calculated to represent the expected range of outcomes for a new study.

2.4 | Model Evaluation

Model fit was evaluated using Akaike Information Criterion (AIC), goodness-of-fit (GOF) plots, and estimates of parameter precision to guide model selection. Statistical significance for covariate inclusion was determined using a p-value cutoff of < 0.05.

2.5 | Model Simulations

The final models were applied to simulate HBsAg loss rates for Peg-IFNα monotherapy and Peg-IFNα + NA combination therapy in a hypothetical phase 3 trial population, demonstrating the utility of MBMA as a virtual control arm to support regulatory applications and optimize trial design. Baseline population characteristics were derived from summary-level statistics of the B-Clear phase 2b trial, which was not included in model development, to represent a relevant phase 3 population [21]. The B-Clear trial enrolled adults with chronic HBV infection for at least 6 months and HBsAg levels > 100 IU/mL. Participants receiving NA therapy were required to have stable regimens, HBV DNA < 90 IU/mL, and alanine aminotransferase (ALT) ≤ 2× the upper limit of normal (ULN). Those not on NA therapy were required to have HBV DNA > 2000 IU/mL and ALT ≤ 3× ULN.

Simulations were performed with $N = 100{,}000$ replicates, where each replicate represents a resampling of the model parameters. Specifically, fixed effects were drawn from their multivariate normal distribution (based on estimated means and variance–covariance matrix), and random effects were sampled from $N\left(0, \sigma^2_n\right)$. This structure reflects both parameter uncertainty and between–study–strata–arm variability. The resulting simulated distributions of outcomes enabled robust estimation of control arm event rates and facilitated exploration of key trial design parameters, including sample size and statistical power.

3 | Results

3.1 | Systematic Literature Review Search Result, Study Selection and Study Characteristics

Database searches identified 2865 records, of which 126 unique primary studies (120 journal articles and 6 conference abstracts) were included for data extraction after screening (Figure S1). For the MBMA, studies were further filtered based on the availability of HBsAg loss data at EOT and/or 24 weeks post-treatment, excluding those with non-standard Peg-IFNα dosing, PP results only, missing baseline HBeAg status, or non-standard HBsAg loss definitions. This yielded 45 studies (52 study-strata, 83 study-strata-arms) for the EOT model and 28 studies (35 study-strata, 58 study-strata-arms) for the 24-week post-treatment model (Table 1). Some studies contributed to both subsets if they reported both endpoints.

The EOT model included 11,493 participants across 83 study-strata-arms, of which 63 were from randomized controlled trials (RCTs) and the remainder from prospective cohorts, retrospective cohorts, or single-arm trials. Four studies provided stratified results by HBeAg status and baseline HBsAg. The 24-week model included 4267 participants across 58 study-strata-arms, of which 43 were from RCTs, 8 from prospective cohorts, 3 from retrospective cohorts, and 3 from single-arm trials. Three studies provided stratified results by HBeAg status, baseline HBV DNA, and baseline HBsAg.

3.2 | Base and Treatment Effect Models

In the base models, which estimated a single overall treatment effect without distinguishing between monotherapy and combination therapy, the average probability of HBsAg loss at end of treatment (EOT) was 6.7% (95% prediction interval [PI]: 0.9%–36.7%), and 6.7% (95% PI: 0.3%–63.7%) at 24 weeks

TABLE 1 | Summary of study characteristics for hepatitis B surface antigen (HBsAg) loss analyses at end of treatment (EOT) and 24 weeks post-treatment.

Characteristics	EOT HBsAg loss	24-week HBsAg loss
Number of studies	45	28
Number of study-strata	52	35
Number of study-strata-arms	83	58
Number of trial participants	11,493	4267
Treatment distribution (Peg-IFNα vs. Peg-IFNα + NA)	RCTs: 33 vs. 30	RCTs: 19 vs. 14
	Prospective cohorts: 6 vs. 4	Prospective cohorts: 7 vs. 6
	Retrospective cohorts: 3 vs. 0	Retrospective cohorts: 1 vs. 2
	Single-arm trials: 2 vs. 5	Single-arm trials: 2 vs. 7

Abbreviations: EOT, end of treatment; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue; RCT, randomized controlled trial.

post-treatment. These wide PIs reflect both parameter uncertainty and between-trial variance, the latter quantified as 1.11 (EOT) and 2.54 (24 weeks) on the logit scale.

Introducing separate drug effects for Peg-IFNα monotherapy and Peg-IFNα + NUC combination therapy shifted the estimated average probabilities modestly higher, but with overlapping PIs. At EOT, the average predicted probabilities were 7.6% (95% PI: 0.8%–36.0%) for Peg-IFNα and 9.8% (95% PI: 1.0%–42.2%) for Peg-IFNα + NUC. At 24 weeks post-treatment, corresponding estimates were 2.7% (95% PI: 0.3%–62.7%) and 3.6% (95% PI: 0.4%–69.4%). Between-trial variance remained largely unchanged from the base models, indicating that distinguishing drug regimens alone did not meaningfully account for heterogeneity.

3.3 | Covariate Testing and Final Models

After inclusion of covariates, Peg-IFNα monotherapy was associated with an estimated HBsAg loss rate of 8.5% (95% PI: 2.3–27.7) at EOT and 11.1% (95% PI: 2.7–36.6) at 24 weeks post-treatment, while Peg-IFNα + NA combination therapy was associated with 11.7% (95% PI: 3.1–35.5) at EOT and 14.1% (95% PI: 3.4–43.4) at 24 weeks (Table 2). These estimates represent outcomes for the reference population, defined as HBeAg-negative participants with baseline HBsAg of 3 $\log_{10}$ IU/mL receiving 48 weeks of Peg-IFNα.

Eight covariates were tested for their association with HBsAg loss: baseline HBsAg, Peg-IFNα treatment duration, baseline HBeAg status, age, gender, race, study design (RCT vs. non-RCT), and continuation of NA after Peg-IFNα cessation (24-week model only). In the EOT model, three covariates were significant: baseline HBsAg ($p < 0.0001$), Peg-IFNα treatment duration ($p = 0.005$), and baseline HBeAg status ($p = 0.007$; Table 2). In the 24-week post-treatment model, two covariates were significant: baseline HBsAg ($p < 0.0001$) and Peg-IFNα treatment duration ($p = 0.0002$). No significant associations were observed for age, gender, race, study design, or continuation of NA.

The magnitudes of covariate effects were similar across models. For each $\log_{10}$ unit increase in baseline HBsAg, the odds of achieving HBsAg loss decreased by 79%. Each additional week of Peg-IFNα treatment increased the odds of HBsAg loss by 1.3% at EOT and 3.1% at 24 weeks. In the EOT model, HBeAg-positive participants showed higher rates of HBsAg loss than HBeAg-negative participants, with odds more than twofold greater (OR = 2.37).

Inclusion of treatment and covariate effects substantially reduced between-trial variance (σ_η^2). Specifically, between-trial variance decreased from 1.112 to 0.484 in the EOT model, a 56.5% reduction; and from 2.544 to 0.572 in the 24-week model, a 77.5% reduction (percent reduction computed as above). Prediction intervals correspondingly narrowed compared with the base models (Figure 1). Treatment differences between Peg-IFNα monotherapy and Peg-IFNα + NA combination therapy persisted after covariate adjustment, with both treatments represented across study designs (Table 1).

In Table 2, untransformed estimates are regression coefficients on the logit scale. For drug effects, these were transformed to probabilities of HBsAg loss in the reference population. For covariates, transformed estimates are expressed as odds ratios, reflecting the multiplicative effect of each covariate on the odds of HBsAg loss.

3.4 | Model Simulations

Using the simulation approach described in the Methods, the final models generated HBsAg loss rate estimates for hypothetical phase 3 trial populations (Table 3). These simulations incorporated both parameter uncertainty and between-trial variability, as reflected across 100,000 replicates.

HBsAg loss rates were estimated for trial populations with integer baseline HBsAg values ranging from ≤ 2 to ≤ 5 $\log_{10}$ IU/mL, assuming a standard 48-week Peg-IFNα treatment duration. Baseline HBsAg and HBeAg inputs were derived from a representative phase 2b trial population [21].

TABLE 2 | Parameter estimates for the final hepatitis B surface antigen (HBsAg) loss models at end of treatment (EOT) and 24 weeks post-treatment.

Parameter	Estimate (logit)	Transformed estimate	%RSE	95% PI	*p*	Interpretation
EOT model						
Drug effect (Peg-IFNα)	−2.37	8.54%	7.7	2.3–27.7	<0.001	8.5% HBsAg loss in reference population (HBeAg–, baseline HBsAg 3 $\log_{10}$ IU/mL, 48 weeks Peg-IFNα).
Drug effect (Peg-IFNα + NA)	−2.02	11.7%	10.3	3.1–35.5	<0.001	11.7% HBsAg loss in reference population (HBeAg–, baseline HBsAg 3 $\log_{10}$ IU/mL, 48 weeks Peg-IFNα + NA).
Peg-IFNα treatment duration (per week, ref. = 48 weeks)	0.0133	OR 1.013	32.9	1.00–1.02	0.005	Each additional week increases odds of HBsAg loss by 1.3%.
Baseline HBsAg (per $\log_{10}$ IU/mL, ref. = 3)	−1.57	OR 0.21	15.5	0.13–0.33	<0.001	Each 1 $\log_{10}$ IU/mL increase reduces odds of loss by 79%.
HBeAg status (ref = negative)	0.863	OR 2.37	34.7	1.34–4.17	0.008	HBeAg+ participants had higher HBsAg loss rates (18.1% vs. 8.5% for Peg-IFNα; 23.8% vs. 11.7% for Peg-IFNα + NA).
Between-trial variance	0.484	—	—	—	—	Variance on logit scale.
24-week post-treatment model						
Drug effect (Peg-IFNα)	−2.08	11.1%	9.1	2.7–36.6	<0.001	11.1% HBsAg loss in reference population (baseline HBsAg 3 $\log_{10}$ IU/mL, 48 weeks Peg-IFNα).
Drug effect (Peg-IFNα + NA)	−1.81	14.1%	11.9	3.4–43.4	<0.001	14.1% % HBsAg loss in reference population (baseline HBsAg 3 $\log_{10}$ IU/mL, 48 weeks Peg-IFNα).
Peg-IFNα treatment duration (per week, ref. = 48 weeks)	0.0303	OR 1.03	24.6	1.02–1.05	<0.001	Each additional week increases odds of HBsAg loss by 3.1%.
Baseline HBsAg (per $\log_{10}$ IU/mL, ref. = 3)	−1.58	OR 0.21	13.0	0.14–0.30	<0.001	Each 1 $\log_{10}$ IU/mL increase reduces odds of loss by 79%.
Between-trial variance	0.572	—	—	—	—	Variance on logit scale.

Note: Transformed estimates are expressed as probabilities for drug effects and odds ratios for covariates.
Abbreviations: %RSE, relative standard error; EOT, end of treatment; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue; OR, odds ratio; PI, prediction interval.

Model diagnostics (Figures 2 and 3) indicated good overall performance. Individual predictions closely followed the line of unity, and weighted residuals showed no systematic trends when plotted against either population-predicted HBsAg loss or baseline HBsAg levels. These findings suggest that the final models were unbiased across the observed continuum of HBsAg loss responses and adequately captured the influence of baseline HBsAg.

3.5 | Application of MBMA in In Silico Trials Simulated Using a Mechanistic Hepatitis B Model

The MBMA results on HBsAg loss at EOT and 24 weeks post–IFN-α cessation were used to support in silico trials of chronic hepatitis B (CHB) therapies simulated with a mechanistic mathematical model of HBV infection. Specifically, the MBMA provided baseline HBsAg distributions and treatment response rates for calibrating virtual patient cohorts, ensuring alignment with real-world clinical data.

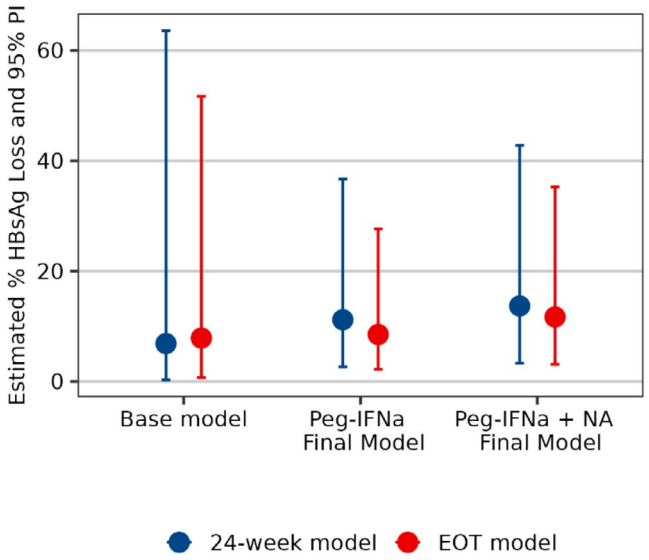

FIGURE 1 | Estimated hepatitis B surface antigen (HBsAg) loss at end of treatment (EOT) and 24 weeks post-treatment from the base and final covariate models, using data from Peg-IFNα monotherapy and Peg-IFNα plus NA therapy. Points show median predictions; error bars indicate 95% prediction intervals reflecting between-trial variability.

For virtual cohorts calibrated with baseline HBsAg levels of 2485 IU/mL (treatment-naive) and 2081 IU/mL (NA-suppressed), the MBMA estimated HBsAg loss rates of 15.1% (95% prediction interval [PI] 11.7%–19.3%) for Peg-IFNα monotherapy and 19.1% (95% PI 14.1%–25.4%) for Peg-IFNα+NA combination therapy in treatment-naive patients. These rates served as benchmarks for validating the in silico trials, which predicted HBsAg loss rates of 17.9% (95% PI 15.5%–20.2%) for Peg-IFNα monotherapy and 25.8% (95% PI 23.3%–28.4%) for Peg-IFNα+NA in naive virtual patients, demonstrating consistency with the MBMA (18).

These applications underscore the utility of MBMA for informing and validating mechanistic models, highlighting its role in advancing model-informed drug development for CHB.

4 | Discussion

This study represents the first model-based meta-analysis (MBMA) to quantify HBsAg loss with Peg-IFNα–based regimens in chronic hepatitis B (CHB). By integrating data from 45 studies for the EOT model and 28 studies for the 24-week post-treatment model, we identified baseline HBsAg, treatment duration, and HBeAg status (EOT only) as significant predictors of response. Incorporating these covariates reduced between-trial variance on the logit scale from 1.11 to 0.48 (58.1% reduction) in the EOT model and from 2.54 to 0.57 (77.6% reduction) in the 24-week model, narrowing prediction intervals while retaining good model fit. These findings establish baseline HBsAg and treatment duration as actionable predictors that can inform patient selection and study design.

Functional cure has become the preferred endpoint for new CHB therapies because of its link to reduced liver disease progression [10, 12, 13]. This MBMA quantifies probabilities of HBsAg loss

TABLE 3 | Simulated Peg-IFNα ± NA HBsAg loss rate at EOT and 24-weeks post-treatment following 48 weeks of therapy ($n = 100{,}000$ replicates).

Treatment group	HBeAg positive (%)	HBsAg criteria ($\log_{10}$ IU/mL)	Mean BL HBsAg ($\log_{10}$ IU/mL)	EOT HBsAg loss % (95% PI)	24-week post-treatment HBsAg loss % (95% PI)
Peg-IFNα monotherapy	27	≤5	3.5	5.1 (1.3–17.9)	5.4 (1.2–21.0)
	23	≤4	3.2	7.7 (2.0–25.2)	8.4 (2.0–29.8)
	14	≤3	2.6	16.5 (4.6–45.2)	19.1 (4.8–52.8)
	0	≤2	1.9	34.5 (10.4–70.5)	41.6 (12.3–78.4)
Peg-IFNα + NA combination	31	≤5	3.3	7.1 (1.9–23.7)	6.8 (1.5–25.3)
	30	≤4	3.2	10.6 (2.8–32.5)	10.4 (2.4–35.2)
	20	≤3	2.6	21.9 (6.2–54.3)	23.0 (5.9–59.0)
	0	≤2	1.9	42.7 (13.7–70.5)	47.5 (15.0–77.7)

Abbreviations: BL, baseline; EOT, end of treatment; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue; PI, prediction interval.

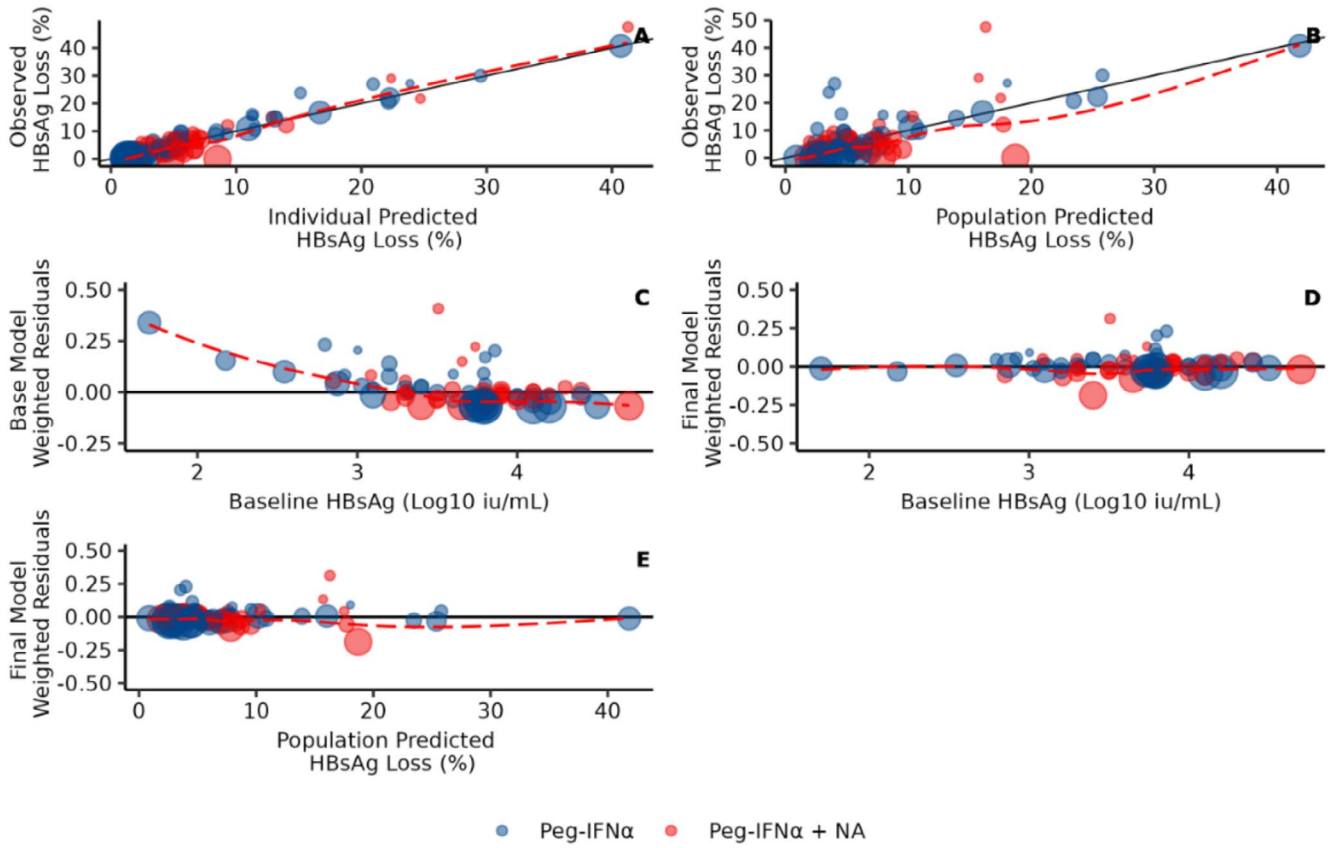

FIGURE 2 | Goodness-of-fit for the hepatitis B surface antigen (HBsAg) loss model at end of treatment (EOT). (A) Observed versus individual-predicted HBsAg loss with the line of unity (black solid). (B) Observed versus population-predicted HBsAg loss with the line of unity (black solid). (C) Base model weighted residuals versus baseline HBsAg (Log_{10} IU/mL). (D) Final model weighted residuals versus baseline HBsAg (Log_{10} IU/mL). (E) Weighted residuals versus population-predicted HBsAg loss. Panels C–E include a reference line at $y = 0$ (black solid). All panels include a LOESS fit (red dashed). Data points represent Peg-IFNα monotherapy (blue) or Peg-IFNα plus NA therapy (red); point sizes reflect the number of subjects per study–strata–arm.

under Peg-IFNα monotherapy and Peg-IFNα + NA combination therapy, offering a reference framework for phase 3 trial design. In particular, patients with lower baseline HBsAg and longer treatment duration had a greater likelihood of response, consistent with biological rationale [7]. These predictors can guide enrichment strategies, control-arm benchmarking, and sample size estimation [14].

Beyond direct trial applications, MBMA has translational utility. Cortés-Ríos et al. (2025) employed our estimates to calibrate in silico CHB trials, aligning virtual patient outcomes with real-world data and reproducing the inverse relationship between baseline HBsAg and functional cure [18]. Such integration highlights MBMA as a bridge between empirical evidence and mechanistic modeling, advancing model-informed drug development in CHB.

Despite these advances, important limitations remain. The analysis relied on aggregated published data, with missingness for HBV genotype, baseline HBV DNA, and baseline ALT restricting covariate evaluation. Prior studies have shown that genotype and ALT strongly influence Peg-IFNα response [15, 16], and low baseline HBsAg has consistently predicted higher loss rates across cohorts, including the EVEREST project [15, 17, 22]. Reported outcomes have ranged from ~17% at 2 years in HBeAg-negative patients treated with Peg-IFNα and adefovir to > 50% at 48 weeks in NA-suppressed HBeAg-negative patients with baseline HBsAg < 1500 IU/mL [15, 17, 22]. Race, often a proxy for genotype, was not significant in our analyses, likely reflecting the predominance of Asian studies where genotypes B and C are most common [23, 24]. Additional factors such as HBV DNA [24–26], higher ALT [24, 25], younger age [24, 27], and female sex [24, 27] have been associated with response in Peg-IFNα studies, but were not significant in this analysis, possibly due to data limitations.

Although Peg-IFNα use has declined in most regions [28], its immunomodulatory properties remain relevant when combined or sequenced with new therapies. Profound viral suppression and HBsAg decline alone may not ensure durable seroclearance, but Peg-IFNα may augment functional cure when used with NAs or HBsAg-reducing agents such as small interfering RNAs or antisense oligonucleotides. Ongoing studies are evaluating whether Peg-IFNα add-on or switch strategies optimize HBsAg loss and durability. This MBMA provides quantitative context for such studies, addressing regulatory considerations highlighted in recent HBV cure guidance [29, 30].

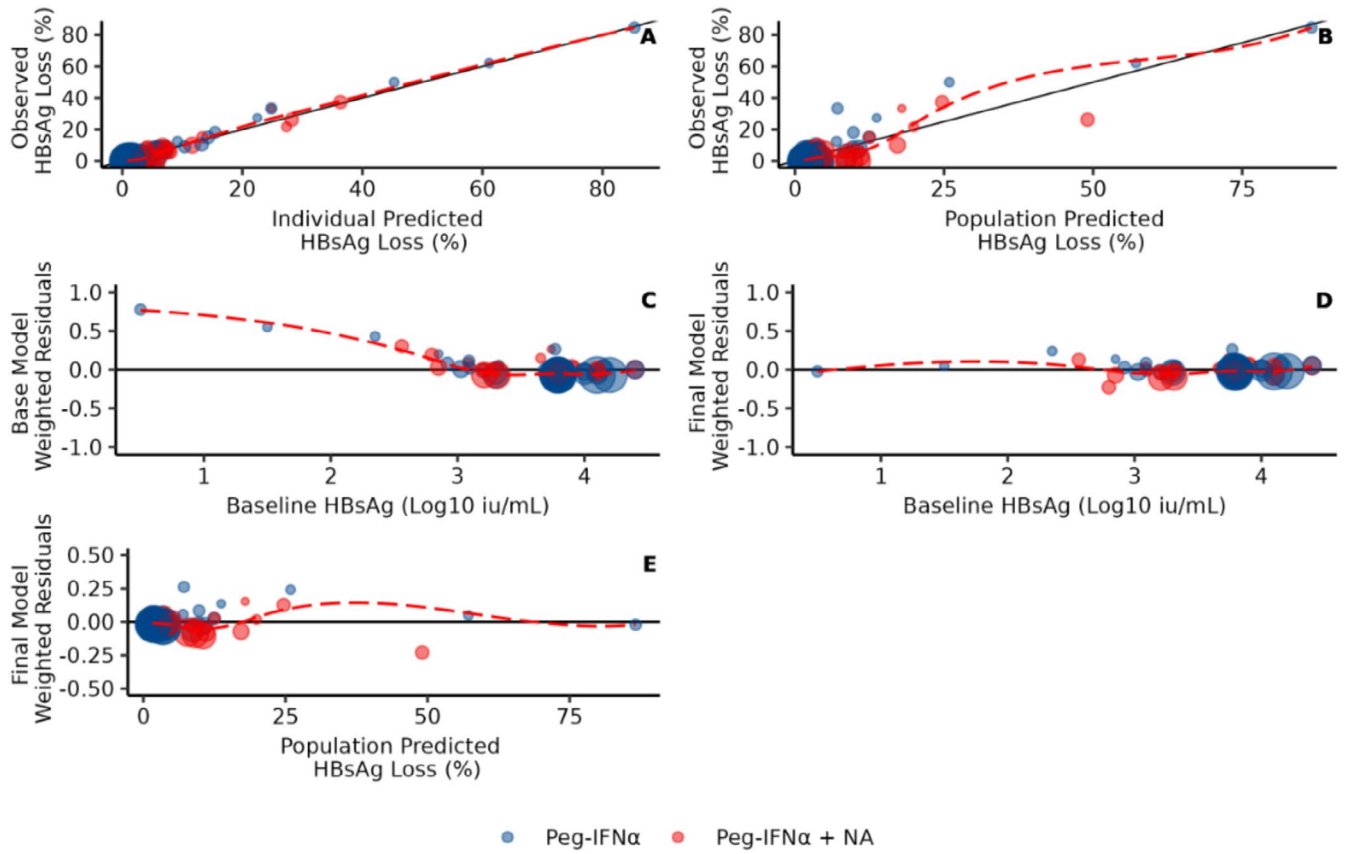

FIGURE 3 | Goodness-of-fit for the hepatitis B surface antigen (HBsAg) loss model at 24 weeks post-treatment. (A) Observed versus individual-predicted HBsAg loss with the line of unity (black solid). (B) Observed versus population-predicted HBsAg loss with the line of unity (black solid). (C) Base model weighted residuals versus baseline HBsAg (Log_{10} IU/mL). (D) Final model weighted residuals versus baseline HBsAg (Log_{10} IU/mL). (E) Weighted residuals versus population-predicted HBsAg loss. Panels C–E include a reference line at $y = 0$ (black solid). All panels include a LOESS fit (red dashed). Data points represent Peg-IFNα monotherapy (blue) or Peg-IFNα plus NA therapy (red); point sizes reflect the number of subjects per study–strata–arm.

Finally, while traditional meta-analyses have assessed HBsAg loss as a prognostic factor for outcomes such as hepatocellular carcinoma [31], this study uniquely applies MBMA to quantify HBsAg loss with Peg-IFNα regimens, filling a key gap in functional cure research. By providing a predictive framework for HBsAg loss, this analysis sets a benchmark for future studies and supports the development of curative strategies for CHB, advancing global HBV elimination goals [1–6, 8, 9, 11].

5 | Conclusion

This MBMA provides an evidence-based framework for predicting HBsAg loss in patients treated with Peg-IFNα-based regimens, highlighting baseline HBsAg levels, HBeAg status, and treatment duration as key predictors of response. While the inclusion of these covariates substantially reduced between-trial variability, a large proportion of heterogeneity remained unexplained, underscoring the need for additional data on factors such as HBV genotype, baseline ALT, and longitudinal virological markers. By quantifying predictors of HBsAg loss, this analysis supports patient selection strategies, informs clinical trial design, and establishes a foundation for model-informed drug development in CHB. Future work incorporating more granular data will be essential for refining predictive models and advancing the pursuit of functional cure.

Author Contributions

N.J.H. wrote the manuscript (all authors contributed to reviewing the manuscript and gave final approval for the version to be published); N.J.H., M.L.Z., A.N., M.M., D.T., S.A.D., J.D., and V.G. designed the research; N.J.H., V.G., A.M., A.K., and K.K. performed the research; N.J.H., M.L.Z., and V.G. analyzed the data. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published.

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Conflicts of Interest

N.J.H., A.N., S.A.D., J.D., M.M., and D.T. are employees of GSK and hold financial equities in GSK. V.G. was an employee of GSK and held financial equities in GSK at the time of this study. A.K. and K.K. are employees of Bridge Medical. A.M. has received consulting fees from GSK. M.L.Z. is an employee of Certara and received consulting fees from GSK.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** psp470164-sup-0001-Supinfo.docx.